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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/766,362	01/19/2001	Solomon S. Steiner	PDC 119	8907

23579 7590 05/20/2005

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ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 05/20/2005

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/766,362
Filing Date: January 19, 2001
Appellant(s): STEINER ET AL.

Patrea L. Pabst
Reg. No. 31,284
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 15 February 2005.

RD

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences, which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1-5, 7-12, 14-18, 20 and 21 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

A substantially correct copy of appealed claims 1-5, 7-12, 14-18, 20 and 21 appears on pages 14-16 of the Appendix to the appellant's brief. The minor errors are as follows:

In appealed claims 5, 12 and 18, a duplicate of the term "diketopiperazine" appears in the claims.

(9) Prior Art of Record

5,503,852	*STEINER et al.*	*04-1996*
5,690,954	*ILLUM*	*11-1997*

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

- Claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17 and 18 are rejected under 35 U.S.C. §103(a) over Steiner *et al.* (US Pat. No. 5,503,852).
- Claims 3, 8, 10, 16, 20 and 21 are rejected under 35 U.S.C. §103(a) over Steiner *et al.* (US Pat. No. 5,503,852) as applied to claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17 and 18 above and further in view of Illum (US Pat. No. 5,690,954).

This rejection is set forth in a prior Office Action, mailed on 07/15/04.

Claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steiner *et al.* (US Pat. No. 5,503,852).

Steiner *et al.* teach drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are formed in the presence of the drug to be delivered and are between 0.1 to 10 microns in diameter and whereby the microparticles are used for diagnostic applications for imaging of the nasal tract (see reference col. 4, lines 30-55); (col. 10, lines 25-49); (col. 13, lines 13-24) and abstract.

According to Steiner *et al.,* biologically active agents having therapeutic, prophylactic or diagnostic activities can be delivered and include active agents, such as hormones, vasoactive agents, anesthetics or sedatives, steroids, decongestants, antivirals, antisense, antigens, antibodies and the like (col. 10, lines 25-49).

Steiner *et al.* teach a system based upon diketopiperazine or one of its substitution derivatives, including *diketomorpholines and diketodioxanes*. The diketopiperazine synthetic intermediates are preferably formed by cyclodimerization to form diketopiperazine derivatives at elevated temperatures under dehydrating conditions, functionalized on the side chains, and then precipitated with drug to be incorporated into microparticles (see abstract; col. 4, lines 49-67; col. 7, lines 8-11).

The protective material, the diketopiperazines, are not biologically active and do not alter the pharmacologic properties of the therapeutic agents (col. 11, lines 1-3).

The instant invention is drawn to a composition for the nasal administration of a drug in dry powder form for administration to the nasal region, whereby the dry powder comprises microparticles having an average particle size of between 10 and 20 microns and comprising drug and diketopiperazines. There is no significant distinction observed between the instant invention and the prior art since the prior art teaches drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are between 0.1 to 10 microns in diameter and are used for nasal applications. Hence, the instant invention is rendered unpatentable over the prior art of record.

Claims 3, 8, 10, 16, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steiner *et al.* (US Pat. No. 5,503,852) as applied to claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17 and 18 above and further in view of Illum (US Pat. No. 5,690,954).

Steiner *et al.*, as delineated above, teach drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are formed in the presence of the drug to be delivered and are between 0.1 to 10 microns in diameter and whereby the microparticles are used for diagnostic applications for imaging of the nasal tract (see reference col. 4, lines 30-55); (col. 10, lines 25-49); (col. 13, lines 13-24) and abstract.

According to Steiner *et al.*, biologically active agents having therapeutic, prophylactic or diagnostic activities can be delivered and include active agents, such as hormones, vasoactive

agents, anesthetics or sedatives, steroids, decongestants, antivirals, antisense, antigens, antibodies and the like (col. 10, lines 25-49).

Steiner *et al.* do not explicitly teach the selective antihistamines.

Illum ('954) teaches a drug delivery system for nasal administration of an active drug in dry powder form wherein the drug delivery system comprises microsphere particles formed of active drugs that include *antihistamines*, vasoconstrictors, anti-inflammatory agents and anesthetics whereby the composition is administered in the form of a dry powder having a particle size of from about 10 microns to about 100 microns (see reference column 5, line 14 through col. 6, line 53); (col. 9, lines 24-61).

Suitable active drugs disclosed are anti-inflammatory agents, vasoconstrictors, anesthetics (analgesics) and antihistaminic agents. Antihistaminic agents are diphenhydramine hydrochloride, *chloropheniramine maleate* and clemastine. The microspheres are administered via the nasal route using a nasal insufflator device. Examples of these are already employed for commercial powder systems intended for nasal application (e.g., Fisons Lomudal System); (col. 8, line 44 through col. 9, line 60).

Illum teaches that the drug to be administered to a mucosal surface such as the nose, eye, etc., can be administered as a powder and can also be administered in the form of a colloidal particle comprising a microsphere system(col. 5, line 14-26).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the combined teachings of Illum within Steiner *et al.*, because Illum teaches a nasally administered drug delivery system and device comprising various active agents

that include vasoconstrictors, anesthetics (analgesics) and antihistaminic agents, among others and similarly, Steiner *et al.* teach drug delivery systems for the mucosal tract that comprise microparticles and microencapsulation for drugs such as vasoactive agents, anesthetics, decongestants, antivirals and the like. The expected result would be an improved and effective nasal administration microparticulate drug delivery system, as similarly desired by the Applicant.

(11) Response to Argument

Rejection of claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17 and 18 under 35 U.S.C. 103(a) over Steiner *et al.* (US Pat. No. 5,503,852).

First and foremost, Appellant argues, "Steiner does not disclose drug delivery systems in a form suitable for nasal administration. Steiner does not disclose dry powder formulations. Steiner does not mention nor suggest a composition of microparticles having an average size between 10 and 20 microns. In contrast, Steiner discloses administering smaller microparticles, with average diameters between 0.1 and 10 microns for oral or intravenous delivery. Steiner does not provide the necessary motivation to one of ordinary skill in the art to modify its particles so that they are suitable for nasal administration."

Appellant's arguments have been considered but were not found persuasive. As delineated above, Steiner *et al.* teach drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are formed in the presence of the drug to be delivered and are between 0.1 to 10 microns in diameter and whereby the microparticles are used

for diagnostic applications for imaging of the nasal tract (see reference col. 4, lines 30-55); (col. 10, lines 25-49); (col. 13, lines 13-24) and abstract. In response to applicant's argument that 'Steiner does not disclose drug delivery systems in a form suitable for nasal administration', Applicant's arguments were not persuasive since the limitation 'suitable for nasal administration' is a future intended use limitation and a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 370 F.2d 576, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 312 F.2d 937, 939, 136 USPQ 458, 459 (CCPA 1963). Moreover, Steiner *et al.* recognize and teach microparticles that bind to mucosal membranes are particularly preferred for diagnostic applications, especially for imaging of the nasal tract (col. 13, lines 18-21). Therefore, Steiner *et al.* suggest the desirability of incorporating the formed drug microparticles for nasal (mucosal) applications. Appellant's argument that 'Steiner does not disclose dry powder formulations' is not persuasive since the formulation of Steiner is a microparticulate (*i.e.*, powder) formulation. Appellant argues, 'Steiner does not mention nor suggest a composition of microparticles having an average size between 10 and 20 microns'. While Steiner *et al.* do not explicitly teach microparticles having an average size 'between 10 and 20 microns', Steiner *et al.* do teach microparticles that have diameters between 0.1 to 10 microns (col. 4, lines 35-40). It is noted that the particles of Steiner having a particle size of 10 microns would be retained in the mucosal cavity for sufficient drug delivery. The Examiner points out that the 'between about 10 microns' is above 10 and

above 10 is not a patentable difference unless Applicant establishes 'between about 10' as a critical lower maximum size limitation. A review of the instant specification indicates that Formulations I and II on pages 13 and 14, respectively, have particles with micron sizes that are less than 10 microns. Specifically, Formulation I on page 13 demonstrates that *10%* of particles had a particle size of only *3.15* microns. Similarly, Formulation II on page 14 demonstrates that *10%* of particles had a particle size of only *2.99* microns. Additionally, Example 5 at page 15 recites 'diketopiperazine particles of *10* microns in diameter'. Therefore, this clearly establishes that the 'between 10 microns' claimed by Applicants is not a critical lower maximum particle size limitation. The instant specification (Formulations I, II and Example 5) demonstrates that significant amounts of particles had a particle size less than 10 microns. Ample motivation is provided by Steiner *et al.* to incorporate their particles, which have a particle size between 0.1 to 10 microns, into drug formulations that are suitably administered for nasal or mucosal applications. The 10 micron-sized particles, in particular, would be retained in the nasal cavity of a patient.

Rejection of claims 3, 8, 10, 16, 20 and 21 under 35 U.S.C. 103(a) over Steiner *et al.* (US Pat. No. 5,503,852) in view of Illum (US Pat. No. 5,690,954).

Secondly, Appellant argues, "Steiner does not disclose antihistamines. Steiner does not disclose drug delivery devices for nasal administration. Steiner does not disclose spray drying and does not mention or suggest a composition of microparticles having an average size between 10 and 20 microns. Illum describes improving the bioavailability of high molecular weight drugs that are administered to the nasal cavity for systemic delivery. Illum discloses

microparticles with a size range between 10 and 100 microns. Illum does not disclose or suggest the inclusion of diketopiperazines in the delivery system and does not suggest the selection of particles having a narrow size range of between 10 and 20 microns."

The Examiner was not persuaded by these arguments. Admittedly, Steiner *et al.* do not disclose antihistamines, however, Illum was relied upon for the teachings that it is well known in the art to incorporate particles formed of antihistamines as the preferred active substance for nasally administered formulations. The particles can be administered via the nasal route using a nasal insufflator device. Illum further teaches a selective antihistamine (*i.e.*, chlorpheniramine) as in instant claims 3, 10 and 16 (see col. 9, lines 48-55). Appellant's argument that 'Steiner does not disclose drug delivery devices for nasal administration' is not persuasive since Steiner *et al.* teach drug delivery systems based on the formation of diketopiperazine microparticles and teach that the particles are particularly preferred for diagnostic applications, especially for imaging of the nasal tract (col. 13, lines 18-21). In reference to Applicant's arguments that 'neither spray drying, nor microparticles having an average size between 10 and 20 microns' is taught by Steiner, Examiner notes that the secondary reference of Illum overcomes and remedies these deficiencies of Steiner *et al.*, by teaching dry powder formulations administered to mucosal surfaces (i.e., nose, eye, etc.), whereby the microparticles have a particle size of from about 10 microns to about 100 microns (col. 5, line 14 – col. 6, line 16). Appellant's argument that 'Illum does not disclose or suggest the inclusion of diketopiperazines' is not persuasive since Illum was not relied upon for the teaching of diketopiperazines, but rather was relied upon for the teaching of the obviousness of utilizing antihistamines as the drug of choice for nasal applications. Moreover, the primary reference of Steiner *et al.* initially meets the limitation requirement of

employing diketopiperazines in mucosal treatment applications. The argument that 'Illum does not suggest the selection of particles having a narrow size range of between 10 and 20 microns' was not persuasive since the particles of Illum are taught to be in the size range of between 10 and 100 microns. This size range clearly encompasses the 'between 10 and 20 microns' claimed by Applicant. The 'between 10 microns' and above taught by Illum indicates that the particles would be sufficiently retained in the nasal cavity.

Next, Appellant argues, "Neither Steiner nor Illum provides a person of ordinary skill in the art with the motivation to combine these references nor is there any indication of a reasonable likelihood of success. Steiner discloses oral or intravenous delivery of small microparticles having sizes ranging between 0.1 and 10 microns. In contrast, Illum is directed to particles with larger diameters, ranging between 10 and 100 microns, which may be administered to the nasal mucosa for drug delivery. There is no disclosure or suggestion in Steiner to modify its particles so that they are larger and Illum does not suggest the selection of particles having a narrow size range of between 10 and 20 microns. There is no suggestion in Steiner to modify its particles so that they can be administered in a dry powder form to the nasal mucosa. Illum does not suggest modifying its bioadhesive microparticles to include diketopiperazines and not require the formation of a gel."

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5

USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Steiner *et al.* teach drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are formed in the presence of the drug to be delivered and are between 0.1 to 10 microns in diameter and whereby the microparticles are used for diagnostic applications for imaging of the nasal tract (col. 4, lines 30-55); (col. 10, lines 25-49); (col. 13, lines 13-24) and Abstract. Steiner *et al.* do not teach antihistamines. Illum was relied upon for the teaching that it is well known to incorporate antihistamines as the active drug material for nasal applications. Illum teach that suitable antihistamines include chlorpheniramine (col. 9, lines 48-52). Illum further teaches that the particles are administered in the form of a powder by spraying (col. 4, lines 13-14). Illum also teaches that the microspheres should be of a size between 10 and 100 microns (col. 6, lines 14-15). Therefore, ample motivation is provided by the prior art to use the particles formed of antihistamines taught by Illum within the particles of Steiner *et al.* Both references suggest and teach drug particles of a suitable size range that would be sufficiently absorbed and retained in the mucosal cavity. Moreover, Applicants have not established that the 'between 10 microns' claimed by Applicants is a critical lower maximum particle size limitation. A review of the specification (Formulations I and II, pages 13 and 14) indicates that 10% of particles had a particle size that was less than 10 microns. Even further, Example 5 at page 15 recites 'diketopiperazine particles having a particle size of *10* microns in diameter'

Appellant argues, "Illum discloses a broad range of diameters for the particles and does not suggest particles having a narrow size range of between 10 and 20 microns. Illum discloses

that microsphere delivery systems through the nasal mucosa must be bioadhesive and contain absorption enhancers to increase the bioavailability of the drug to be delivered. In contrast, Applicants delivery system requires the use of diketopiperazines and does not require the formation of a gel."

Appellant's arguments were not persuasive. As delineated above, Illum teaches that the microspheres should be of a size between 10 and 100 microns (col. 6, lines 14-15). This particle size range clearly meets and encompasses the 'between 10 and 20 microns' claimed by Applicant. Appellant's argument that 'the delivery systems of Illum contain absorption enhancers to increase bioavailability and requires the formation of a gel' is not persuasive since the instant 'comprising' claim language permits the presence of additional components or additional steps asides from those recited. Furthermore, Applicants have not demonstrated that the addition of absorption enhancers taught by Illum would be detrimental to the formulation. Illum teaches that the absorption enhancers enhance the uptake of active drug materials, especially from the nasal cavity. Regarding the requirement of diketopiperazines argued by Applicant, it is pointed out that the primary reference of Steiner *et al.* explicitly teaches drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine. Substitution derivatives including diketomorpholines and diketodioxanes are also taught (col. 4, lines 49-67 and col. 7, lines 8-11).

Lastly, Appellant argues, "Steiner does not disclose nor suggest all of the elements of the claimed invention. The formulations that are disclosed would not be suitable since they must be

suspended in an aqueous medium for injection. Neither Steiner nor Illum provides a person of ordinary skill in the art with the motivation to combine these references."

The Examiner was not persuaded by these arguments. The prior art recognizes solutions versus dry formulations to be equivalent and one of ordinary skill in the art would be fully capable of choosing either form (solution or dry) depending on the future intended method of administration. See in particular, Illum at column 5, lines 14-17, wherein Illum teaches that the 'drug to be administered to a mucosal surface in the gastrointestinal tract, the eye, genital tract or the nose or lung could be administered as a viscous *solution,* a suspension *or powder* or colloidal particle'. Therefore, ample motivation is provided by Steiner *et al.* and Illum to utilize their combined teachings to arrive at the instant invention. The prior art teaches the use of the same ingredients (*i.e.*, diketopiperazines, antihistamines), used for the same field of endeavor (*i.e.*, mucosal applications) to treat the same problems (*i.e.*, retention of drug in nasal cavity) as that desired by Applicants. Since the prior art recognizes and explicitly teaches drug delivery systems based on the formation of diketopiperazine microparticles and teaches the microparticles to be in a suitable size range (between 0.1 and 10 microns -Steiner & between 10 and 100 microns –Illum), the instant invention when taken as a whole, is rendered *prima facie* obvious to one of ordinary skill in the art.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Humera N. Sheikh – Group 1615

hns
May 13, 2005

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